

## COPD exacerbations

Hurst, John R.; Bafadhel, Mona; Bolton, Charlotte E.; Quint, Jennifer K.; Sapey, Elizabeth; Wilkinson, Tom M.A.

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# Exacerbation of COPD: transforming outcomes through research

John R Hurst, Mona Bafadhel, Charlotte E Bolton, Jennifer K Quint, Elizabeth Sapey and Tom MA Wilkinson. All authors contributed equally to this work.

"Would you tell me, please, which way I ought to go from here?"

"That depends a good deal on where you want to get to." [1].

The time has come for a revolution in the prevention and mitigation of exacerbations in chronic obstructive pulmonary disease (COPD). In the UK, recent national audit data demand urgent attention. Admissions to hospital for COPD exacerbations have risen by 13% since 2008, to 115,000 /year [2]. In-patient mortality is 4%, and a further 3% will die and 24% will be re-admitted to hospital within 30 days of discharge [2]. There are unexplained variations in care-quality that exaggerate the health inequalities already associated with COPD. And these concerning statistics on secondary care admissions represent just a small proportion of the overall burden of exacerbations.

At the most basic level we still have a problem with terminology. It is impossible to have an exacerbation of COPD if a person does not have COPD, yet the lack of access to - or willingness to access –confirmatory quality-assured diagnostic spirometry results at the time a patient presents with exacerbation is of considerable concern [2]. The definition and diagnostic criteria for COPD exacerbation remain imperfect. The GOLD strategy document defines exacerbation as a change in symptoms requiring additional therapy [3]. In everyday-practice exacerbation is a clinical diagnosis of exclusion, suggested by changes in symptoms, but only made when the clinician has considered and where appropriate excluded other causes of symptom changes in a patient with known COPD. Despite considerable effort, there remains no diagnostic test for exacerbation that is sufficiently sensitive or specific to rule-in and rule-out exacerbation from other causes of symptoms changes, or to differentiate exacerbation of COPD from COPD in the stable state [4].

Current interventions to treat COPD are inadequate. Remarkably, there have been no new interventions to treat COPD exacerbations in our entire professional lifetime of over 20 years. The evidence for oral steroids is weak and based on outcomes that do not focus on the patient – typically speed of improvement in lung function [5]. Avoidable morbidity from over-use of steroids is considerable and, as commonly employed in ‘rescue packs’, it is known that not all patients are able to self-manage appropriately [6]. Over-use of antibiotics risks development of anti-microbial resistance in the individual, and in our societies. We have no reliable methods to differentiate bacterial, viral or environmental exacerbations at the point of care and, in any case, we have no effective anti-viral interventions to treat rhinovirus – the commonest single cause of COPD exacerbations. Our fundamental understanding of the biology of a COPD exacerbation is incomplete, limiting therapeutic developments. Although it is now accepted that exacerbations are not all the same and can be ‘phenotyped’ [7], initial evidence to support a stratified medicine approach - better targeting of steroids (using blood eosinophils [8]) and/ or antibiotics (using biomarkers such as CRP, procalcitonin or indeed sputum colour) have not been translated into routine clinical practice. Anecdotally, patients have long-acting bronchodilators stopped in

preference to nebulised short-acting drugs. Patients still experience iatrogenic oxygen toxicity [2]. Attention to co-morbidities is poor despite the increasing prevalence of an ageing, multi-morbid patient population with poly-pharmacy. We welcome the move to a rolling UK national COPD audit programme [2] as a tool for quality improvement – specialist review at the front door and an evidence-based bundle of interventions prior to discharge – but also needed is a revolution in the evidence base for exacerbation treatment: both better use of existing interventions and the rapid development and testing of new interventions (anti-inflammatories, for example) based upon a deeper understanding of fundamental disease mechanisms.

Better communication and closer working across hospital clinicians, community-based teams, and primary care may be one way to mitigate the risks of repeat admission. An exacerbation event should be used as an opportunity to review the patient's preventative strategies. There are data to support the idea that the timing of exacerbation events is not random, with a higher-risk for repeat exacerbation in the recovery period from a first [9]. Reducing the risk, and consequences arising from a first hospitalised exacerbation therefore appears particularly important and thus how best to reduce the risk of readmission is a major unanswered problem. Patients susceptible to frequent exacerbations, a relatively stable phenotype [10], experience an excess burden of disease.

We do, at least, have interventions that can to some degree reduce the risk of exacerbations. Current strategies achieve, at most, a 25% reduction suggesting that 75% of events remain unmitigated. Even this assumes appropriate targeting, however it is clear that exacerbation reduction interventions remain poorly focused with considerable under- and over-treatment and therefore avoidable morbidity and excess health-care cost. Additional challenges include translating the benefit from interventions seen in high-quality randomised trials to the real life multi-morbid patients that dominate clinical practice. High value interventions include vaccinations and pulmonary rehabilitation [11], supplemented by judicious use of pharmacotherapy, which for many people should now be based on one or more long-acting bronchodilators [3]. Evidence to support robust identification of groups most likely to benefit (or not) from inhaled corticosteroids remain in evolution, and careful targeting of novel therapies is of increasing importance with the emergence of evidence to support the use of biologicals including anti-eosinophil strategies.

At a global scale the challenges managing COPD and COPD exacerbations are even greater. 90% of COPD deaths occur in low- and middle-income countries (LMIC), where much COPD is associated with household air pollution from biomass and solid fuels, in addition to that associated with tobacco smoke exposure [12]. There is very little known about the biology of exacerbations in biomass COPD, or about the most appropriate strategies for exacerbation prevention and treatment in LMIC. Clearly, in all settings, exposure reduction initiatives provide the best opportunity to reduce the burden of COPD in future generations.

We argue that with an ageing and multi-morbid population, a revolution in the care and prevention of COPD exacerbations is urgently required – across all health-care settings. Clinicians should not accept exacerbations as inevitable. We need new, high-quality evidence to better target existing interventions, incompletely effective as they are, and the ability to rapidly test and implement new exacerbation prevention and treatment strategies - in real-world settings. Research funding must be directed to better understand the fundamental biology of exacerbations if we are to develop new therapies. The UK COPD national audit programme, when appropriately resourced in individual units, can measure the implementation of interventions and help assess impact on outcomes. This unique tool for quality improvement provides learning opportunities for other health-systems. Only by acting urgently, with renewed enthusiasm, can we hope to reduce the current inadequate and

unequal care for people living with COPD, and improve exacerbation experience and outcomes. We know where we are going. We know how to get there. It is now time for all of us to act.

#### **Conflict of Interest Statement:**

Dr Hurst holds UK Medical Research Council (MRC) grant support, and reports grants to his institution, personal fees and non-financial support from pharmaceutical companies that make medicines to treat COPD, outside the submitted work. Dr Bafadhel reports holds a postdoctoral fellowship from National Institute for Health Research (NIHR), and the views expressed here are those of the author and not necessarily those of the UK National Health Service (NHS), the NIHR or the Department of Health. Dr Bafadhel also reports personal fees from pharmaceutical companies that make medicines to treat COPD, outside the submitted work. Dr Bolton reports grants from MRC/ABPI, and reports grants to her institution, personal fees and non-financial support from pharmaceutical companies that make medicines to treat COPD, outside the submitted work. Dr Quint reports grants from MRC, the British Lung Foundation (BLF) and the Wellcome Trust, and grants and personal fees from pharmaceutical companies that make medicines to treat COPD, outside the submitted work. Dr Sapey reports grants from MRC, the Wellcome Trust, NIHR, and BLF and reports grants to her institution from pharmaceutical companies that make medicines to treat COPD, outside the submitted work. Dr Wilkinson holds MRC and NIHR grant support, and reports grants to his institution, personal fees and non-financial support from pharmaceutical companies that make medicines to treat COPD, and a directorship of MyMHealth Ltd, outside the submitted work.

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